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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,611	08/26/2008	Steven Siegel	P-7562-US	7210

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EXAMINER	
AL-AWADI, DANAH J	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
02/17/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/585,611	SIEGEL ET AL.	
	Examiner	Art Unit	
	DANAH AL-AWADI	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *21-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

1. Receipt is acknowledged of Applicant's amendments and remarks filed 11/22/2010. The Examiner acknowledges the following:

Claims 1, 3, 4, 9, 11, 15, and 16, have been amended.

INFORMATION DISCLOSURE STATEMENT

2. No new Information Disclosure Statement has been submitted for review.

WITHDRAWN OBJECTIONS/REJECTIONS

3. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

4. In light of Applicant's amendments, particularly for claim 1, which adds the limitations that the polymer is PLGA at a concentration of about 40-90% (w/w) and the drug risperidone, 9or 9-OH-risperidone, at a concentration of about 10-60% (w/w), the following rejections have been newly added:

NEW REJECTIONS-Necessitated by Amendment

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 16, depends from claim 2 which ultimately depends on claim 1. Claim 1 recites the drug is risperidone or 9 –OH-Risperidone or active metabolite thereof. Claim 16 recites other drugs that the drug comprises which are different to Risperidone or 9-OH-Risperidone. It is unclear what the drug is intended to be.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence

Claims 1-13, and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al. (US 2002/0179096) in view of Kino et al. (US Patent 5, 871, 778).

Siegel et al. teaches a surgically implantable drug delivery system for long-term delivery of the antipsychotic drug – haloperidol (see Abstract); (page 2, paragraphs 0019-0021). The implantable delivery system contains a biodegradable polymer, preferably a lactide-glycolide copolymer (page 1, paragraph 0002); (page 3, paragraph 0023). Siegel et al. discloses an implant of polylactide-co-glycolide, one phase of which has slow release, the other having a faster release (paragraph 0024). The implant is specifically indicated for the treatment of psychotic disorders ((paragraph 0021) and (0032)). The implantable delivery system comprising the antipsychotic drug haloperidol provides superior treatment outcomes due to improved medication adherence. The implants are designed to last for months to years. Advantages of the implants include lower dosing, steady state serum drug levels and increased bioavailability (page 2, paragraph 0022). The implants can be removed and thus offers a degree of reversibility (page 1, paragraph 0010).

It is noted that Siegel does not teach their implant to be a "rod-shaped" structure. However, the particular shape of the implant would be based on personal preference and/or the particular intended use of the implant. Moreover, an effective shape can be determined by one of ordinary skill in the art in order to provide an optimal outcome. The particular shape of the implant being claimed does not render a patentable distinction over the disclosure of Siegel who clearly recognizes and teaches an implantable drug delivery system comprising an antipsychotic drug (haloperidol) in combination with biocompatible polymers, such as polylactic acid and

polyglycolic acid, whereby the implant is removable and is effective for the treatment of psychotic disorders and conditions.

Thus, the instant invention would be prima facie obvious to one of ordinary skill in the art, given the teachings of Siegel.

It would have been obvious to the skilled artisan at the time the invention was made to have administration of two formulations because it is routine in the art to administer drugs to the same patient in multiple different dosage forms in order to achieve a particular therapeutic affect.

With regards to the limitations "whereby administering said first and second formulation results in therapeutic circulating levels of said drug, for a period of about 14-120 days, thereby being a method of treating a nervous system disorder", until some material difference(s) in the properties of the composition are demonstrated, said limitation is considered by the Examiner to be directed towards the drug formulation which is instantly claimed. Furthermore, the limitation having circulating therapeutic levels of the drug is future intended use as a result of the composition being implanted and is given little patentable weight. Absent evidence to the contrary, it is expected that the formulation would achieve the same circulating levels as claimed.

Siegel teaches subcutaneous delivery (paragraph (0013)). Furthermore, Siegel teaches implantable drug delivery devices (abstract). These devices are fully capable of being implanted subcutaneously.

Siegel teaches that the implant comprises a PLGA (polylactic acid to polyglycolic acid) ratio of 75:25 (paragraph (0024)). Therefore, as per pending claim 9, the implants vary in terms of drug concentration, polymer composition, or combination thereof. Siegel also teaches the biodegradable polymer also comprises about 50 to 100% polylactide and 0 to 50% polyglycolide

(paragraph (0023)). The range reads and falls within the range of said polymer 40-90%. The drug, haloperidol is disclosed to be in the preferred range of from about 20% to about 40% (paragraph (0023)). Also see Examples 4-5. This range reads on the range of therapeutic drug of 10-60%.

Siegel teaches that the therapeutic drug is present in an amount of 30%-60% of the mass of the implant (paragraph (0023)).

With regards to administration of the formulations, it would have been obvious to one of ordinary skill in the art to administer the formulation within 1-24 hours, cyclically, or within 160-200 days in order to achieve an additive synergistic effect of the drugs while prolonging the effect of the drug.

Siegel teaches the antipsychotic drug – haloperidol, used to treat psychotic disorders such as schizophrenia (paragraph 0032). Siegel discloses risperidone as a known antipsychotic drug (paragraphs (0009) and (0014)). While Siegel does not teach the antipsychotic drug – risperidone, for use in the invention, both of these drugs - haloperidol and risperidone are well-known effective psychotic medications useful for the treatment of psychotic disorders and would have equivalent efficacy, as evidenced by Kino.

Kino teaches a sustained release microsphere preparation produced by combining an antipsychotic drug such as haloperidol or risperidone with polymers such as polylactic acid, polyglycolic acid or the like (see column 2, line 45 - col. 3, line 16); Claims 5 and 8. The preparation of Kino aims to improve the maintenance therapy and increase patient compliance with hydrophobic antipsychotic drugs (col. 2, lines 15-29); (col. 2, lines 5-20). Additional antipsychotic drugs are disclosed at column 2, lines 45-55.

It would have been obvious to one of ordinary skill in the art in order to employ any antipsychotic drug, particularly risperidone, such as that taught by Kino, within the delivery systems of Siegel. One would do so with a reasonable expectation of success because Kino teaches preparations with the incorporation of antipsychotic drugs such as risperidone, haloperidol and the like which are known for their therapeutic efficacy of mental conditions (i.e., schizophrenia, bipolar disorder). The preparations enable improved patient compliance and effectively provide for the treatment and therapy of mental disorders and psychotic conditions. The expected result would be an improved drug delivery system comprised of antipsychotic agents for effectively combating psychotic disorders.

7. Claim 13 and 14 rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al. (US 2002/0179096) and Kino et al. (US Patent 5, 871, 778) as applied to claims 1-13, 15-20 above, and further in view of Sidman (US Patent 4, 352, 337).

Siegel does not disclose a rod shaped implant having a diameter of about 1 to 2mm, a length between about 10 and about 40 nm, or a combination thereof, however, Sidman teaches a rod-shaped implantable drug delivery device (col. 10 line 62-64 Fig 2). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the implants as taught by Siegel into the shape of rods because it would have been obvious to one of skill in the art to form the implants in a shape that is desirable for ease of administration.

Sidman further teaches that the implant has a diameter between 2-4mm(col. 22 lines 45-40).

RESPONSE TO ARGUMENTS

8. Applicant argued, "Nowhere does Siegel describe or teach this combination of claimed features. Rather, Siegel relates to haloperidol loaded with polylactide or lactide-co-glycolide copolymer. Although Kino describes a laundry list of active materials including risperidone, it provides no data or support for how much of each active ingredient can be loaded into each biodegradable polymer. Kino does not teach or suggest how to arrive at the claimed 10%-60% risperidone and 40%-90% of the biodegradable polymer."

Applicant's arguments have been considered but were not found persuasive. In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and KSR International Co. v. Teleflex, Inc., 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, the primary reference of Siegel teaches a surgically implantable drug delivery system for long-term delivery of the antipsychotic drug – haloperidol. While Siegel does not teach the antipsychotic drug – risperidone, the secondary reference of Kino was invoked for this teaching that the use of risperidone for the treatment and therapeutic efficacy of mental conditions such as schizophrenia and bipolar disorder, is well known. The preparations of Kino enable improved patient compliance and effectively provide for the treatment and therapy of mental disorders and psychotic conditions. As a result, one of ordinary skill in the art would substitute the haloperidol of Siegel with the risperidone of Kino, whereby ample motivation is provided based on the

combination of references to utilize risperidone, known for its effectiveness for the treatment of mental conditions and disorders. Applicant's argument that "Kino relates to a microcapsule which is not an implant" was not persuasive since the primary reference initially recognizes and teaches a surgically implantable drug delivery device as presently claimed. Moreover, the secondary reference of Kino was relied upon for the teaching of the specific drug (risperidone) and thus, is ample for all that it suggests and teaches to one of ordinary skill in the art.

The argument that "Kino describes a laundry list of active materials including risperidone but provides no data or support for how much of each active ingredient can be loaded into each biodegradable polymer" was not rendered persuasive. The fact that the reference recognizes use of risperidone for the treatment of mental conditions such as schizophrenia and bipolar disorder is ample to meet Applicant's claimed limitations. With respect to the amount of biodegradable polymer, note that the implant of Siegel comprises a PLGA (polylactic acid to polyglycolic acid) ratio of 75:25 (paragraph 0024); (Example 1). The biodegradable polymer can also comprise about 50 to 100% polylactide and 0 to 50% polyglycolide (paragraph 0023). Also see Examples at pages 4-5. This range reads on, falls within and overlaps with the range of said polymer (polylactide) of 40-90% in instant claim 1. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). With respect to the amount of active ingredient that can be loaded into each biodegradable polymer (10-60%), while the instantly claimed drug percentage/range is not explicitly taught, the Examiner points out that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence

indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine suitable ranges or percentages of drug through routine or manipulative experimentation, to obtain the best possible results, as these are variable parameters attainable within the art. Furthermore, no unexpected or superior results have been observed in the instant amounts or ranges claimed. The prior art clearly teaches a similar formulation having similar ingredients, used for the same field of endeavor, as that desired by Applicants. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

Applicant argued, "In the subject application, surprisingly and unexpectedly, the invention changes the matrix degradation and affects the release rates. As stated in the application, higher risperidone loading concentration stabilizes the system, slowing the release rate."

Applicant's arguments have been considered but were not found persuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., slower release rates, stability) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims are silent in terms of any specific rates of release or dissolution profiles that would distinguish over the release pattern of

drug disclosed by the prior art. When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

CONCLUSION

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CORRESPONDENCE

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Danah Al-awadi whose telephone number is (571) 270-7668. The examiner can normally be reached on 9:00 am - 6:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DA/
Examiner, Art Unit 1615

/Humera N. Sheikh/
Primary Examiner, Art Unit 1615